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(54) Title: COMPOSITIONS AND METHODS FOR TREATING RESPIRATORY DISORDERS

(57) Abstract

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold–like, allergy, sinus and/or flu symptoms by administering a safe and effective amount of a composition comprising naproxen along with cetirizine.

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COMPOSITIONS AND METHODS FOR TREATING RESPIRATORY DISORDERS

TECHNICAL FIELD

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms by administering a safe and effective amount of a composition comprising naproxen or a related compound along with cetirizine or a related compound.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying affliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

Early symptoms may be minimal with only mild malaise, sore throat and nasal complaints. With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of illness and progress to maximum severity by the second or third day. Along with nasal symptoms may come sore, dry or scratchy throat and hoarseness and cough. Other symptoms may include mild burning of the eyes, loss of smell and taste, a feeling of pressure or fullness in the sinuses or ears, headache, and vocal impairment. Fever can occur, but is uncommon. Influenza infection generally includes fever, often of sudden onset and persisting for several days, and with great severity; generalized aches and pains; fatigue and weakness; and chest discomfort.

At present, only symptomatic treatment is available for the common cold. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect

costs, based on the amount of loss in wages because of restricted activity are substantially higher.

Exemplary prior art formulations for treatment of cough, cold, cold-like, allergy, sinus and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

The use of non-steroidal anti-inflammatory drugs to combat inflammation and attendant pain is accepted medical practice. The non-steroidals are commonly employed to relieve pain and inflammation associated with, for example, bursitis, arthritis, headache and the like. Among the most commonly used drugs of the non-narcotic analgesic class of drugs are aspirin, acetaminophen, ibuprofen, ketoprofen, diclofenac and naproxen and their salts (e.g., lysine, arginine, sodium and potassium). Aspirin, acetaminophen and ibuprofen have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multisymptom alleviating compositions. These commercially marketed products generally contain in addition to aspirin, acetaminophen or ibuprofen, one or more antihistaminics, decongestants, cough-suppressants, antitussives and expectorants.

The present inventors have found that selected compositions comprising naproxen along with cetirizine provides improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms, including nasal congestion.

It is therefore an object of the present invention to provide a method for the treatment of cough, cold, cold-like, allergy, sinus and/or flu symptoms in a mammalian organism in need of such treatment comprising administering to such organism the compositions of the present invention. Such symptoms as used herein refer to coryza, nasal congestion, sinus congestion, sinus pain, upper respiratory infections, otitis, sinusitis, etc.

SUMMARY OF THE INVENTION

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms by administering a safe and effective amount of a composition comprising naproxen along with cetirizine.

All percentages and ratios used herein are by weight unless otherwise indicated. Additionally, all measurements are made at 25°C unless otherwise specified.

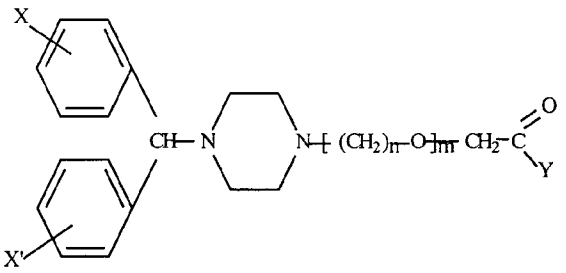
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms by administering a safe and effective amount of a composition consisting essentially of naproxen along with cetirizine.

Cetirizine

The present invention relates to the use of 2-[4-(diphenyl-methyl)-1-piperazinyl]-acetic acids and the amides and non-toxic, pharmaceutically acceptable salts thereof, in compositions also containing naproxen.

Cetirizine and related compounds have the general formula:



wherein

Y is hydroxyl group or an --NH_2 group,

X and X' represents independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,

m is 1 or 2, and

n is 1 or 2, preferably 2, as well as the non-toxic, pharmaceutically acceptable salts thereof.

The term "lower alkoxy" as used herein means residues of both straight and branched chain aliphatic alcohols having from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and the like. The halogen atom is preferably a chlorine or fluorine atom.

The expression "non-toxic, pharmaceutically acceptable salts" are used herein means not only the addition salts of the acids and amides of formula with pharmaceutically acceptable acids, such as acetic, citric, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric and phosphoric acid, but also the pharmaceutically acceptable salts of the acids or formula such as the metal salts (for example sodium or potassium salts), the ammonium salts, the amine salts and the aminoacid salts.

The preferred compounds according to the present invention are:
2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride;
potassium 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetate;
2-[2-[4-[(4-diphenylmethyl)-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride;
2-[2-[4-[(4-fluorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid and its hydrate.

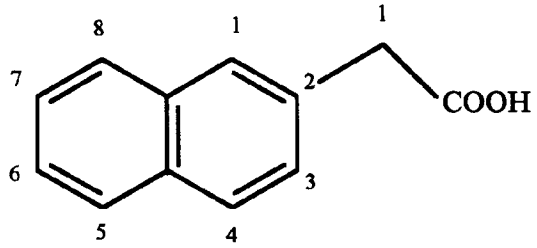
The cetirizine compounds of formula possess interesting pharmacological properties. In particular, they are useful as antiallergic, antihistaminic, bronchodilatory and antispasmodic agents and are used at a level of from about 5 to about 20 mg.

The preferred compounds are 3,4-dihydro-6-fluoro-2-naphthyl-α-methylacetic acid, the aklyl esters thereof wherein the alkyl moiety has 1 to 12 carbon atoms, and the pharmaceutically acceptable addition salts thereof. Particularly preferred are: 3,4-dihydro-6-chloro-2-naphthyl-α-methylacetic acid, the alkyl esters thereof wherein the alkyl moiety has 1 to 12 carbon atoms, and the pharmaceutically acceptable addition salts thereof.

These compounds are described in detail is U.S. Patent 4,525,358, June 25, 1985, incorporated herein by reference in its entirety.

Naproxen

Naproxen and similar compounds are derivatives of 2-naphthylacetic acid, a compound which can be represented by the formula:



The arabic numerals and the alpha symbols indicate the positions used herein in the nomenclature of 2-naphthylacetic acid derivatives. This is a general formula for naproxen and its related compounds.

These are further described in U.S. Patent 3,896,157, incorporated herein by reference in its entirety. Naproxen itself is (S)-6-Methoxy-2-methyl-2-napthaleneacetic acid and preferably the sodium salt.

Naproxen and its related compounds are generally used in amounts of 50 to 660 mg, preferably from about 100 to 330 mg and more preferably from about 150 to about 220 mg.

Additional Pharmaceutical Actives

The compositions of the present invention can also include at least one other pharmacological active selected from the following class: (a) a decongestant, (b) an expectorant (c) an additional antihistamine and (d) an antitussive. The decongestants useful in the compositions of the present invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof. The antitussives useful in the present invention include those such as dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof. The additional antihistamines useful in the present invention include those such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbromphreniramine, triprolidine, azatadine, doxylamine, tripelennamine, cyproheptadine, hydroxyzine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, astemizole, azatadine, azelastine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, and temelastine, their pharmaceutically acceptable salts and mixtures thereof. The expectorants (also known as mucolytic agents) useful in the present invention include glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts, and mixtures thereof. All of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

Additional agents which are found useful in the present compositions are α-agonists such as those disclosed in U.S. Patent 5,478,858, issued December 26, 1995, incorporated herein by reference in its entirety.

Various oral dosage forms can be used, including such solid forms as tablets, caplets, capsules, granules, lozenges and bulk powders and liquid forms such as syrups and suspensions. Controlled release dosage forms which provide a controlled release of these active(s) are also useful. These oral forms comprise a

safe and effective amount, usually at least about 5% of the active components. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95% of the active components. Liquid oral dosage forms preferably contain from about 1% to about 50% and more preferably from about 1% to about 25% and most preferably from about 3% to about 10% of the active components.

Tablets can be compressed, triturated, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flowinducing agents. Also useful are soft gelatin capsules.

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, taste-masking agents, coloring agents, and flavoring agents. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

An additional agent found useful in the present compositions is caffeine. Caffeine has been found to lessen the minor sedating effect of the cetirizine. The level of caffeine use is generally from about 20 mg to about 500 mg, preferably from about 50 mg to about 200 mg, most preferably from about 65 mg to about 100 mg.

In preparing the liquid oral dosage forms, the active component is incorporated into an aqueous-based orally acceptable pharmaceutical carrier consistent with conventional pharmaceutical practices. An "aqueous-based orally acceptable pharmaceutical carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension of the pharmaceutical composition in an aqueous vehicle containing a suitable suspending agent. Suitable suspending agents include

Avicel RC-591 (a microcrystalline-cellulose/sodium carboxymethyl cellulose mixture available from FMC), guar gum and the like. Such suspending agents are well known to those skilled in the art. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the active component and other optional non-active ingredients, the total water content, based on the weight of the final composition, will generally range from about 20 to about 75%, and, preferably, from about 20 to about 40%, by weight/volume.

Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from about 5 to about 25 volume/volume percent and, most preferably, from about 10 to about 25 volume/ volume percent, of the co-solvent.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate, to prolong and enhance shelf life. A highly preferred optional component is caffeine.

METHOD OF TREATMENT

The amount of the pharmaceutical composition administered depends upon the percent of active ingredients within its formula, which is a function of the amount of cetirizine and naproxen and any optional components such as a de congestant, cough suppressant, expectorant, caffeine and/or additional antihistamine required per dose, stability, release characteristics and other pharmaceutical parameters.

Usually from about 1 mg/kg to about 50 mg/kg per day, preferably from about 2 mg/kg to about 30 mg/kg per day and most preferably from about 3 mg/kg per day to about 20 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose, or, preferably, in multiple (two to six) doses repeatedly or sustained release dosages over the course of treatment. Generally, each individual dosage of the pharmaceutical compositions of the present invention range from about 1 mg/kg to about 25 mg/kg, preferably from about 2 mg/kg to about 15 mg/kg and most preferably

from about 3 mg/kg to about 10 mg/kg. While dosages higher than the foregoing are effective to provide relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms, care must be taken, as with any drug, in some individuals to prevent adverse side effects.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

EXAMPLE I

A hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
Naproxen Sodium	220 - 440 mg.
Pseudoephedrine HCl	60 mg. (120 mg. sustained released)
Cetirizine *	5 mg.

Triturate active ingredients and q.s. with lactose to selected capsule size.

* Cetirizine is [2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid.

Administration of one or two the above capsules every four to twelve hours to a human in need of treatment provides improved relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms.

EXAMPLE II

A hard compressed caplet composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
Naproxen Sodium	220 or 440 mg.
Cetirizine	5 mg.
Pregelatinized starch	20.0 mg.
Corn starch	80.0 mg.
Croscarmellose sodium	10.0 mg.
Silicone dioxide, colloidal	1.5 mg.
Stearic acid, TP fine powder	2.0 mg
Sodium lauryl sulfate	0.5 mg
Opadry clear / Colorcon (containing Hydroxypropylmethyl cellulose)	5.0 mg.

Administration of two caplets every twelve hours to a human in need of treatment provides improved relief from cough, cold-like, flu-like and allergic rhinitis symptoms.

EXAMPLE III

A hard compressed tablet composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
Naproxen sodium	220 or 440 mg.
Cetirizine	5 mg.
Microcrystalline cellulose	110 mg.
Povidone	10 mg
Talc	12 mg
Magnesium stearate	2 mg
Opadry clear / Colorcon (containing Hydroxypropylmethyl cellulose)	5.0 mg.

Administration of one of the above tablets every twelve hours to a human in need of treatment provides improved relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms.

EXAMPLE IV

A liquid composition for oral administration is prepared by combining the following ingredients:

Ingredient	% W/V
Naproxen sodium	2.200
Cetirizine	0.050
High Fructose corn syrup (55%)	55.000
Polyethylene Glycol 400	10.000
Propylene Glycol	10.000
Alcohol (95%)	8.500
Sodium citrate dihydrate	0.470
Citric Acid	0.180
Saccharin socium	0.700
Flavor	0.015
Color	0.005
Water, Purified QS	QS to 100%

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, asodium succharin, and actives other than naproxen sodium are added sequentially and dissolved with agitation. The high frucose is then added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the naproxen sodium is added to the alcohol while stirring. The propylene glycol, polyethylene glycol, and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 teaspoonsful) every twelve hours to a human in need of treatment provides improved relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms.

Administration of 20 ml (4 teaspoonsful) every eight to twelve hours to a human in need of treatment provides improved relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for providing improved treatment, management or mitigation of cold, cold-like, allergy, sinus or flu symptoms by administering a safe and effective amount of a composition comprising:
   (a) an analgesic which is naproxen or a related compound or a pharmaceutically acceptable salt thereof; and
   (b) cetirizine or a related compound.

2. A pharmaceutical composition according to Claim 1 wherein said cetirizine or related compound is selected from the group consisting of selected from the group consisting of methyl 4-[1-hydroxy-4-(4-hydroxydiphenylmethyl-1-piperidinyl)butyl]-α,α-dimethylbenzeneacetate, 4-[1-hydroxy--4-(4-hydroxydiphenylmethyl-1-piperidinyl)butyl]-α,α-dimethylbenzeneacetic acid, 1-[p-(2-hydroxymethyl-2-propyl)-phenyl]-4-[4(α-hydroxy-α-phenylbenzyl)-1-piperidinyl]butanol, and mixtures thereof.

3. A pharmaceutical composition according to Claim 2 which contains an additional analgesic agent selected from the group cosisting of ibuprofen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofen and diclofenac.

4. A pharmaceutical composition according to Claim 3 wherein said naproxen or related compound or additional analgesic agent is the amino acid salt and is selected from the group consisting of triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, ornithine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purine, piperazine and piperidine and mixtures thereof.

5. A pharmaceutical composition according to Claim 3 additionally comprising a pharmaceutical active selected from the group consisting of decongestants, expectorants, additional antihistamines, antitussives and mixtures thereof.

6. A pharmaceutical composition according to Claim 5 wherein said additional antihistamine is selected from the group consisting of chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbromphreniramine, triprolidine, doxylamine, tripelennamine, cyproheptadine, carbinoxamine, bromodiphenhydramine, pyrilamine, acrivastine, AHR-11325, phenindamine, astemizole, azatadine, azelastine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and mixtures thereof or pharmaceutically acceptable salts thereof.

7. A pharmaceutical composition according to Claim 5 which comprises the S(+) enantiomer of naproxen or related compound or the additional analgesic agent.

8. A pharmaceutical composition according to Claim 7 wherein said S(+) enantiomer of the additional agent is selected from the group consisting of S(+)-ketoprofen lysinate, S(+)-ibuprofen lysinate and mixtures thereof.

9. A pharmaceutical composition according to Claim 1 which in additionally comprises an α-agonist compound, caffeine, and mixtures thereof.

10. The use of a an analgesic and antihistamine for the manufacture of a medicament for the treatment of sinus pressure, sinus pain, sinus drainage, nasal congestion, cough, cold, cold-like or flu symptoms in a mammalian organism in need of such treatment, said treatment comprising administering to such organism the composition of Claim 1.

INTERNATIONAL SEARCH REPORT

In .national Application No
PCT/IB 98/01339

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	WO 97 04808 A (PROCTER & GAMBLE) 13 February 1997 see page 3, line 27 - page 4, column 18; claims 1,3,4,6-14; examples 3,4 see page 5, line 22 - page 6, line 17 see page 7, line 9-13	1,4-10 1-6,9,10 2,3
Y	US 5 648 358 A (MITRA SEKHAR) 15 July 1997 see column 2, line 26-55; claims 1-3 see column 3, line 1-39; claims 5-15	1-6,9,10
X	US 4 871 733 A (SUNSHINE ABRAHAM ET AL) 3 October 1989 see column 5, line 38-41; claims 1,3,8-11,24-28 see column 6, line 61-66 see column 11, line 37-40	1,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1998	09/12/1998

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In national Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 783 465 A (SUNSHINE ABRAHAM ET AL) 8 November 1988 see claims 1,3,8,22; example 2	1,10
X	WO 95 07103 A (PROCTER & GAMBLE) 16 March 1995 see page 4-5; claims; example 2	1,4-8,10
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/01339

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. national Application No
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